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## **Self-reported health status after solid-organ transplantation**

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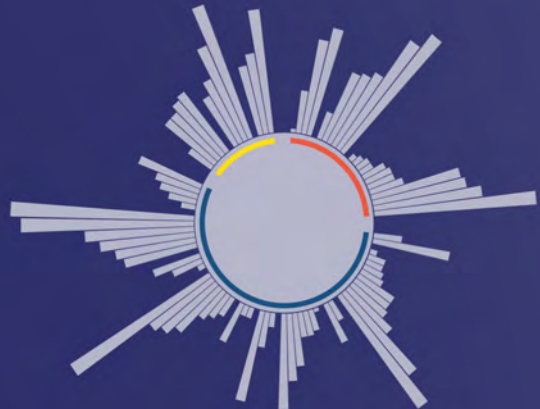
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# CHAPTER 3



## Patient-reported health outcomes in long-term lung transplantation survivors: A prospective cohort study

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## Abstract

During the last 3 decades lung transplantation (LTx) has become a proven modality to increase both survival and health-related quality of life (HRQoL) in patients with various end-stage lung diseases. Most previous studies have reported improved HRQoL shortly after LTx. With regard to long-term effects on HRQoL, however, the evidence is less solid. This prospective cohort study was started with 828 patients who were on the waiting list for LTx. Then, in a longitudinal follow-up, 370 post-LTx patients were evaluated annually for up to 15 years. For all wait-listed and follow-up patients, four HRQoL instruments were administered: State-Trait Anxiety Inventory, Zung Self-rating Depression Scale, Nottingham Health Profile, and a visual analogue scale. Cross-sectional and generalized estimating equations (GEE) analysis for repeated measures were performed to assess changes in HRQoL during follow-up. After LTx, patients showed improvement in all HRQoL domains except pain, which remained steady throughout the long-term follow-up. The level of anxiety and depressive symptoms decreased significantly and remained constant. In conclusion, this study showed that HRQoL improves after LTx and tends to remain relatively constant for the entire life span.

## **Introduction**

Lung transplantation, with a reported median survival of 5.8 years, is currently recognized as a worthwhile modality of treatment for patients with end-stage lung diseases [1]. Over 55,000 transplants have been performed worldwide over the last three decades. This quantitative increase was concurrent with improvements in the physical and mental aspects of health in these patients [1, 2]. The survival rate has increased due to advances in surgical techniques and post-operational care such as guidance on lifestyle and administration of potent anti-microbial agents. Besides the increase in life years, it is important for both patients and health-care providers to assess the effects of transplantation on health-related quality of life (HRQoL).

After lung transplantation, patients encounter challenges such as risk of graft rejection, chronic lung allograft dysfunction such as bronchiolitis obliterans syndrome (BOS), infections and malignancies due to immunosuppression, and side effects of medications [3, 4]. In both the short and long term these issues can also affect their HRQoL. Several studies have been performed with health-outcome measurement instruments that capture a specific element of HRQoL. In the short term, most patients are found to experience meaningful improvements after lung transplantation [5-10]. However, the generalizability of these studies is constrained by methodological problems such as cross-sectional design, short-term follow-up, and small sample sizes. A few longitudinal studies have evaluated HRQoL after lung transplantation [11-14]. The biggest changes they report occur in the early post-transplant period in the domains of physical health and functioning like walking capacity which generally remained constant in subsequent follow-ups. But these studies have methodological problems too: small sample size and inclusion of combined heart and lung-transplant patients. In light of their systematic review, Seiler and colleagues summarized HRQoL and psychological outcomes in patients after LTx and found that “the trajectory beyond 3 years post-transplant appears to remain uncertain, mostly due to the lack of data” [15].

In the present study we describe the trend of HRQoL in a large cohort of lung-transplant patients demonstrated by longitudinal serial annual evaluations up to 15 years after transplantation. We then evaluate the effect of demographic and clinical factors on that trend during the post-transplant period. Our hypothesis was that health improves after transplantation and then remains stable.

## **Methods**

### **Study design**

In a prospective cohort study conducted from 1992 to 2014, all eligible candidates for lung transplantation in the University Medical Center Groningen (UMCG) who gave consent to participate were included in the study. In addition, patients from the University Medical Center Utrecht (UMCU) and Erasmus Medical Center Rotterdam (EMC) were included from 2002 on. Inclusion criteria were candidacy for lung transplantation, age  $\geq 18$ , and sufficient Dutch language skills. Neither patients with previous lung transplantation nor candidates for a combined heart and lung or lung and liver transplantation were included.

The study protocol was approved by the institutional review boards of all 3 centers. Since post-transplant health evaluations are part of standard care at all 3 centers, Dutch legislation did not require ethical approval. The immunosuppression protocol in the

UMCG was Cyclosporine-based from 1992 to 2001; afterwards, it was Tacrolimus-based. All participants received adequate information about the study and were assured that their information would remain confidential. After obtaining informed consent, demographic variables such as age, gender, marital status, working situation, and underlying pulmonary disease were registered.

All patients were asked to fill in two generic and two domain-specific instruments to score their perceived HRQoL. The self-report instruments were first completed upon entering the waiting list for lung transplantation and subsequently upon annual evaluation. The maximum follow-up time in this cohort was 15 years. Forms were sent by postal mail and participants were asked to fill in the instruments themselves at home.

### HRQoL instruments

This study applied two domain-specific HRQoL instruments to evaluate anxiety and depression. Anxiety was measured with the State-Trait Anxiety Inventory (STAI), a 20-item self-report measure in which responses are given on a four-point Likert scale from 4 (always) to 1 (never). The overall score ranges from 20 to 80, with 80 representing the worst possible state of anxiety [16]. Depression was measured with the Zung Self-rating Depression Scale (SDS), a 20-item self-report instrument with a 4-point Likert scale to evaluate the psychological, affective, and somatic symptoms associated with depression. The overall score to be obtained with this instrument ranges from 25 to 100, where high scores indicate severe symptoms [17]. We followed the standard instructions of the Zung and STAI. Accordingly, when calculating overall scores, if the number of missing items was equal or less than 2, we imputed their value by taking the mean of the other items. Overall scores with more than 2 missing items were excluded from the analysis.

In addition, the Nottingham Health Profile (NHP) was used as a generic HRQoL instrument. The NHP is a self-report tool that contains 38 items and measures 6 domains of HRQoL: emotional reactions, social isolation, sleep, pain, energy, and physical mobility. The response categories for each item are 'yes' and 'no'. Separate scores are calculated for each domain and lie between 0 and 100, whereby higher scores represent lower levels of HRQoL. Following the instructions for this instrument, if for an individual patient a response was missing on at least one item, that domain was excluded from the analysis [18].

In addition, patients were shown the visual analogue scale of the EuroQol instrument (EQ-VAS) and asked to choose a number between 0 and 100 to represent their perceived health condition. A higher number indicates better health [19].

### Statistical analysis

Descriptive statistics were used to summarize the patients' demographic and baseline characteristics. Means (standard deviation) were calculated at every follow-up point to chart the trends for the HRQoL domains. Several independent variables were selected on the basis of their clinical relevance and similar previous studies for the purpose of assessing their effect on the trends of HRQoL found in this study. The list consisted of gender, age, working situation, marital status, pre-transplant diagnosis, type of transplant, and type of immunosuppression after transplantation. The independent variables were entered in the analysis as determinants of longitudinal change. Separate analyses were

performed in which the patients were divided in 3 groups based on age (younger than 44, between 45 and 55, and older than 56 years). Graphs were drawn to demonstrate the trend of the scores of the instruments with a 95 percent confidence interval. The scores were reversed on the graphs to demonstrate the increasing trend of HRQoL.

Generalized estimating equations (GEE) models were employed to identify significant determinants of longitudinal changes in HRQoL during the 15-year follow-up time. GEE analysis takes into account the correlation of responses for an individual patient and has many advantages for analyzing longitudinal or repeated measures. This statistical routine is flexible in handling missing data and produces efficient and unbiased regression coefficients ( $\beta$ ) [20]. In this study, the exchangeable working correlation matrix option was used to estimate  $\beta$ s for each independent variable. Level of significance was set at a  $p$  value of less than 0.05. Student's  $t$ -tests were performed to compare the results of our study with data for the general population. All statistical analyses were done with the SPSS 20.0 software package (IBM Corporation, Chicago IL, USA). SigmaPlot version 12.3 (Systat Software, Inc., San Jose CA, USA) was used for drawing the graphs.

## **Results**

### **Patients' participation and demographics**

From 1992 to 2014 a total of 1083 end-stage lung-disease patients became candidates for lung transplantation in the UMCG, UMCU, and EMC. Among them 828 (76%) participated in the study by filling in the instruments the moment they were placed on the waiting list. Some possible reasons for not participating in the study were a lack of interest, a short time between candidacy and surgery, and being too ill. Eventually, 370 (34%) of those initial participants underwent lung transplantation. In addition to those 828 participants, 56 patients (from the original 1083 candidates) filled in the instruments after transplantation for the first time, bringing the total number of participants up to 884 (81%). Figure 1 schematically depicts the inclusion and the number of patients (including percentages of living respondents) who filled in the HRQoL instruments at each time point, the number of patients who died, censored due to the end of study, and lost to follow-up during the 15 years.

The age of patients in this study ranged from 13 to 69 years, with a mean age of 46.6 (11.7 SD) when wait-listed. Two patients were registered on the waiting list at age 13 and 14, but they started to fill in the instruments after they turned 18. A total of 487 (55%) patients were female (Table 1). A large proportion of the participants (30%) had become end-stage lung-disease patients due to chronic obstructive pulmonary diseases (COPD), a smaller share due to cystic fibrosis (CF) (17%).

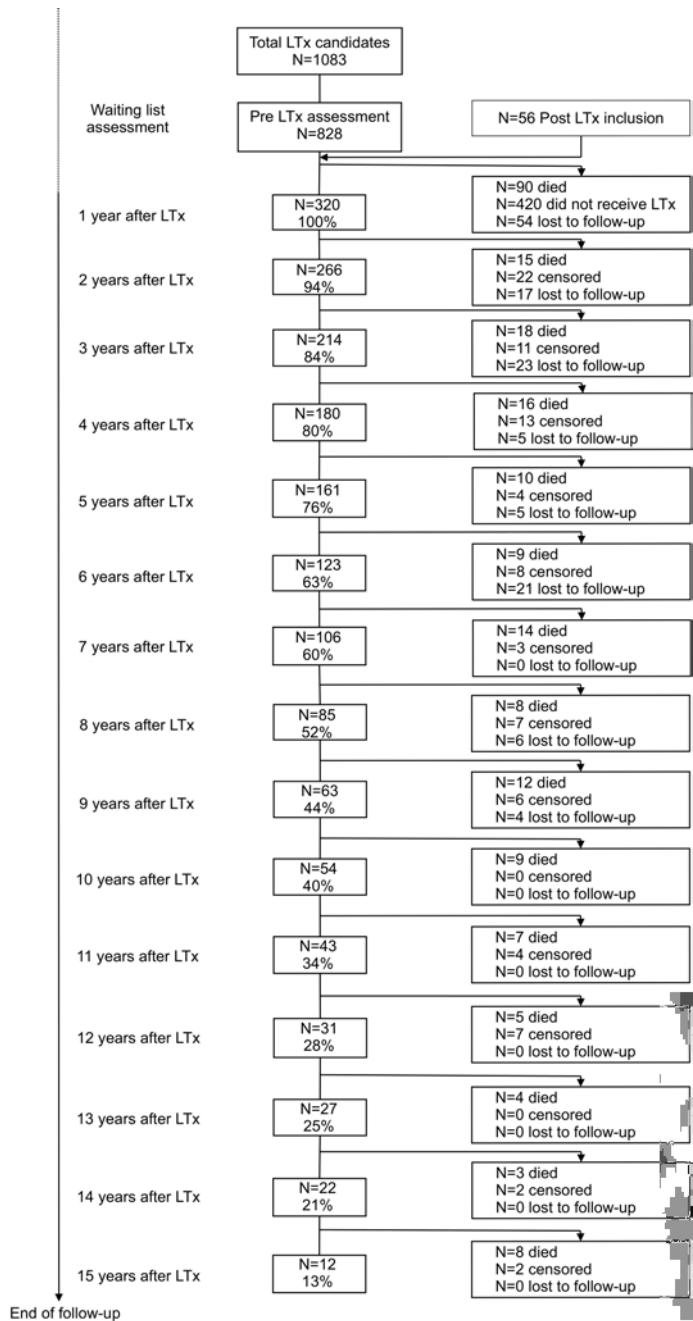


Figure 1. Scheme of study inclusion and follow-up (LTx, lung transplantation).

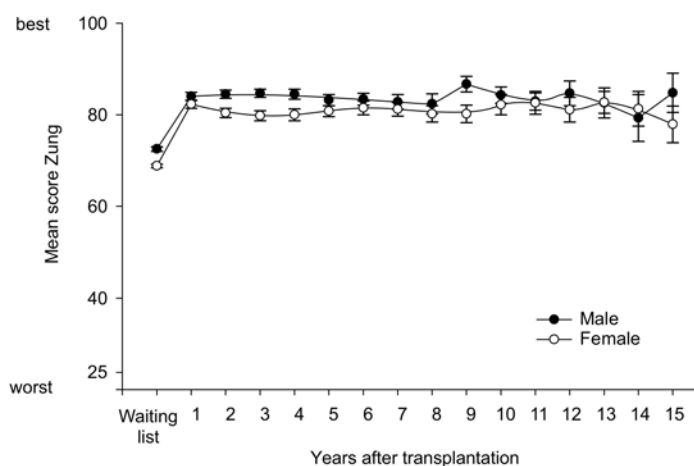
**Table 1.** Sociodemographic characteristics of the study population

Characteristics	N	Percent
Waiting list		
Gender		
Male	397	44.9
Age years mean (range)	46.6	13-69
Marital status (have partner)	599	67.8
Working or studying	215	24.3
Underlying medical disease		
Alpha1-anti trypsin deficiency	109	12.3
Cystic fibrosis	155	17.5
COPD	269	30.4
Other	351	39.7
First year after LTx		
Gender		
Male	154	48.1
Age years mean (range)	47.6	19-66
Marital status (have partner)	213	66.6
Working or studying	76	23.8
Underlying medical disease		
Alpha1-anti trypsin deficiency	55	17.2
Cystic fibrosis	48	15.0
COPD	97	30.3
Other	120	37.5
Type of LTx		
Bilateral	199	62.2
Type of immunosuppression		
Tacrolimus	225	70.3

### Baseline differences in HRQoL

In the waiting list assessment, female patients showed significantly higher levels of anxiety and depression than males (Figure 2). Their mean NHP scores on energy and physical activity were also worse (Figure 3). Patients who were working or studying had significantly better STAI and Zung scores ( $38.3 \pm 0.8$  and  $50.6 \pm 0.6$ ) than the non-working group on the waiting list ( $43.2 \pm 0.5$  and  $55.7 \pm 0.4$ ). Those working or studying had better scores on energy, social isolation, and physical activity ( $52.34 \pm 5.3$ ,  $8.90 \pm 2.3$ , and  $35.74 \pm 3.1$ ) compared to the non-working group ( $72.21 \pm 2.7$ ,  $14.62 \pm 1.6$ , and  $55.89 \pm 2.2$ ). Similarly, the working or studying patients reported better VAS scores before the transplantation compared to patients who did not work or study ( $51.1 \pm 2.4$  and  $41.4 \pm 1.5$ ).





**Figure 2.** Reversed mean scores for depressive symptoms (Zung) by gender.

According to the underlying medical disease, patients with cystic fibrosis had the lowest level of anxiety ( $39.1 \pm 0.9$ ), followed by patients diagnosed with alpha 1-anti trypsin deficiency ( $40.5 \pm 1$ ). Patients with COPD had the highest STAI mean score ( $43.9 \pm 0.7$ ). They also had significantly higher levels of depression ( $56.7 \pm 0.6$ ) than patients with cystic fibrosis, alpha 1-anti trypsin deficiency, or other pulmonary diseases ( $52.8 \pm 0.8$ ,  $53 \pm 0.8$ , and  $54.1 \pm 0.5$  respectively).

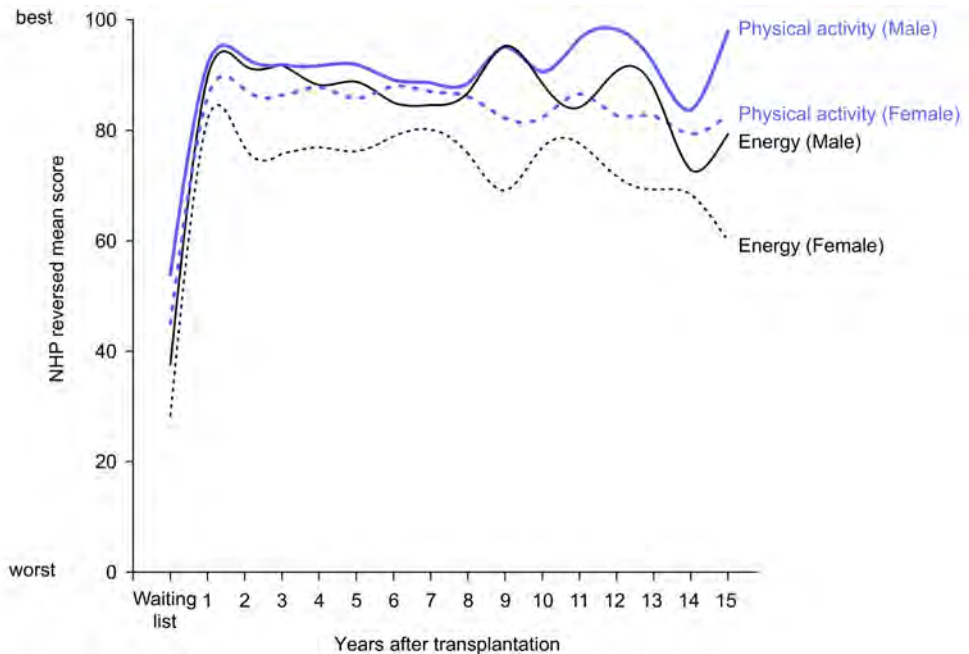
### Patterns of HRQoL after LTx

The STAI and Zung mean scores as well as all domains of the NHP, except for pain, declined sharply immediately after transplantation. Overall, the study population reported a considerably higher perceived health condition (VAS score) compared to the assessment when placed on the waiting list (Table 2). The improvement in HRQoL remained relatively steady from the first year after LTx to the end of follow-up. After transplantation, most patients reported a HRQoL comparable to that of the general population [21]. However, post-transplant patients had a higher level of depression compared to values for the general population sample ( $p < 0.001$ ) [17].

### Patterns of HRQoL after LTx in different groups

GEE analysis was performed to evaluate the longitudinal differences in HRQoL scores on selected independent variables (Appendices 1 and 2). Regarding gender, females showed significantly higher levels of depression than males after LTx ( $p = 0.01$ ) (Figure 2). Similarly, females had worse mean scores on energy level ( $p = 0.009$ ) and physical activity ( $p = 0.012$ ) (Figure 3). Regarding age, patients in all 3 categories showed a significant decline in anxiety and depressive symptoms immediately after transplantation, and that trend continued steadily until the end of follow-up. Patients younger than 44 years had significantly better scores on sleep ( $p = 0.011$ ) and physical activity ( $p = 0.0001$ ).

From the first to the fourth year after transplantation, the lowest STAI scores were found among cystic fibrosis patients and the highest among COPD patients.



**Figure 3.** Reversed mean scores for physical activity and energy domains of HRQoL (NHP) by gender.

However, GEE analysis did not show a significant difference between these diagnostic groups. Comparison of the 4 diagnostic groups showed that patients with CF and alpha 1-anti trypsin deficiency had significantly lower levels of depression ( $p = 0.003$  and  $p = 0.025$ , respectively) than patients with other diagnoses. The perception of overall health was better in the CF and alpha 1-anti trypsin groups, according to their VAS score ( $p = 0.001$  and  $p = 0.016$ ). CF patients also had the lowest scores on energy level ( $p = 0.007$ ), sleep ( $p = 0.001$ ), and physical activity ( $p < 0.001$ ).

The STAI and Zung mean scores of both working/studying and non-working groups decreased considerably one year after the transplantation and remained constant during the post-transplant period. The working/studying group had a statistically significant lower level of anxiety ( $p = 0.024$ ) and depression ( $p = 0.016$ ). This group also had better scores in the physical activity and pain domains of NHP ( $p < 0.001$ ), especially in the first 6 years of the post-transplant period.

Patients who received Tacrolimus for immunosuppression after lung transplantation reported levels of anxiety in our study comparable to those reported by patients who received Cyclosporine ( $p = 0.953$ ). Since the usage of Tacrolimus is part of the newest protocol for patients in our medical centers, the comparison of these groups is only possible for the most recent 11 years. According to the depression, despite the slightly higher level of depressive symptoms in the Tacrolimus group compared to the Cyclosporine group in the first 3 years after LTx, GEE analysis showed a non-significant difference between these two groups during the post-transplant period.

Regarding the type of transplant, unilateral and bilateral lung recipients showed a similar steady trend in STAI and Zung scores during follow-up. Patients who underwent

**Table 2.** Scores on the 4 HRQoL instruments: mean (standard deviation)

	Reference value	MID	Waiting list N=828	Year 1 N=320	Year 5 N=161	Year 10 N=54	Year 15 N=12
STAI	≤37	10	42.1 (11.2)	32.9 (10.8)	33.4 (10.4)	33.4 (10.9)	36.0 (14.0)
Zung	≤33	8-9	54.5 (9.5)	41.8 (10.9)	43.0 (10.4)	41.8 (10.5)	43.1 (10.6)
NHP Energy	<15	n/a	67.5 (35.6)	14.3 (29.9)	17.4 (31.7)	17.5 (30.9)	29.4 (45.9)
NHP Pain	<15	n/a	8.3 (17.7)	7.4 (18.4)	9.1 (22.5)	16.0 (29.4)	16.4 (30.7)
NHP Emotional reactions	<15	n/a	18.3 (21.4)	6.0 (13.4)	6.8 (14.7)	8.6 (18.4)	11.9 (20.0)
NHP Sleep	<15	n/a	25.4 (29.8)	16.4 (26.4)	15.7 (25.4)	18.7 (29.1)	3.5 (11.0)
NHP Social isolation	<15	n/a	13.2 (19.5)	3.2 (9.7)	2.9 (9.0)	4.8 (13.4)	6.1 (10.4)
NHP Physical mobility	<15	n/a	51.0 (26.5)	11.1 (19.8)	11.1 (18.3)	13.6 (18.2)	10.0 (15.7)
VAS	>82	7-10	43.7 (18.5)	78.5 (16.8)	77.7 (17.4)	77.8 (15.5)	74.7 (21.9)

Range of possible scores: STAI, 20 to 80; Zung, 25 to 100; NHP, 0 to 100; and VAS, 0 to 100.  
MID, Minimal important difference.

unilateral transplantation had a better score for pain than the bilateral group in the first year after surgery. This difference was not significant during subsequent years and both groups showed a steady trend over time. Nor was there a significant difference in other domains between these two groups. Unilateral transplant patients had worse VAS scores with an increasing trend during the first 4 post-transplant years compared to the bilateral recipients. The score of both groups became similar in the fifth year and remained constant until the end of follow-up.

## Discussion

The main goal of this study was to describe the long-term HRQoL of lung-transplant recipients up to 15 years after surgery. Lung transplantation is performed in chronic, end-stage lung-disease patients who are at high risk of death (>50%) within two years without transplantation [22]. These chronic diseases considerably reduce the patients' HRQoL. Previous studies have shown that the most noteworthy improvements in HRQoL happen during the first year after transplantation [11, 12]. In our study, we also found that most improvement occurred within the first year in the main domains of HRQoL (psychological, social, and physical) except for the pain domain of NHP, which stayed constant during the whole study period. This finding was predictable, in view of the improvement in lung function during the post-transplant period. Constant use of immunosuppressive drugs after transplantation, as well as the risk of many immunosuppression-related health problems like various cancers and infectious diseases but also side effects such as headache, nausea, tremor and vomiting [3, 23, 24], might in the long-term lead to a decrease in the health condition of the lung recipients.

One of the important findings of this study was that the improvements in the patients' health condition fall largely within the reference values of the general population and

remain almost steady during the next 15 years. This finding also has been observed previously in a study by Kugler and colleagues [25]. In a cohort of 280 LTx patients, they found an overall improvement in perceived HRQoL that brought HRQoL to a level comparable to that of a cohort of healthy controls. Kugler and colleagues found a decline in HRQoL 5 to 6 years after transplantation exclusively among a sub-group of patients with BOS. Some previous studies evaluated the health status of lung-transplant candidates more than 1 year after transplantation and reported a decline in health status [12, 26-28]. However, at a duration of 4 to 10 years, the follow-up period in these studies was relatively short in comparison with our study.

Another finding of our study is that female patients generally had relatively worse HRQoL both before and after transplantation. However, both genders showed significant improvement in HRQoL afterwards. The worse HRQoL among females was predominantly in the physical domains of the NHP, concurring with findings for both healthy people and populations with chronic lung diseases in previous studies [21, 29-33]. According to those studies, this difference in HRQoL is not related to the difference in the severity of the symptoms between males and females. The lower HRQoL among females may be partly explained by the different prevalence of mobility-related disease among males and females. Musculoskeletal disorders and movement impairments are more prevalent in women [34, 35]. Moreover, some studies indicate that women may have higher expectations of medical care and are less satisfied than men after receiving the same treatment [36-38]. Similarly, women might have higher expectations of lung transplantation than men and would expect to resume their social and physical activities sooner. Holding higher expectations might be a source of distress and cause more anxiety and depressive symptoms. Further research with regard to the causal relation between expectations of transplant outcomes, gender, and mental state might be helpful in delivering more personalized care in the future.

In this study patients with cystic fibrosis (CF) generally reported better perceived HRQoL than other patients. Comparison to other patients showed that the CF patients experienced fewer problems with mobility and sleep. This finding is in line with the results of previous studies regarding the influence of baseline diagnosis on HRQoL after transplantation [39-42]. Due to a lifetime of lung disease before LTx, the CF patients could not experience the “full” health that other groups of patients could have enjoyed in earlier stages of life. After LTx, they could enjoy a lifestyle free of respiratory symptoms, which is indeed a reason for a higher HRQoL. Moreover, CF patients are younger than other patients at the time of LTx and generally in better physical condition. In addition, engaging in more diverse activities than older patients, such as returning to work or study, can have a positive effect on their perceived HRQoL.

The overall health condition of patients who worked or studied was better than that of the non-working group, both before and after transplantation. This difference was pronounced in the psychological and social domains of HRQoL. The relationship between having a job and a better perceived HRQoL was also found in previous studies in the general population [43, 44] and other patient populations [45, 46]. Employment is important to the patients as it provides them with an income, opportunities to structure their daily lives, and satisfying social interactions, all of which can affect HRQoL. This finding suggests that working after transplantation might help increase the HRQoL of patients.

By extending the duration of follow-up, the present study makes an important contribution to the body of literature. Previous studies reported discrepancies in the long-term trend of HRQoL among patients after transplantation, but those studies followed patients for only a few years or used a retrospective study design. Due to the multicenter approach, our prospective longitudinal study with long-term post-transplantation follow-up, a relatively large sample size, and homogeneity of the cases regarding single or combined organ transplantation, the results of our study add valuable knowledge to the field and can be used as strong evidence for the long-term effectiveness of lung transplantation with regard to HRQoL. We used two generic and two domain-specific HRQoL instruments to evaluate most aspects of the health condition in our population. When this study was started in 1992, NHP was one of the most well-known instruments to evaluate the health condition of patients. Although this instrument has been applied less frequently in recent years, we decided to continue using it for the latest evaluations to ensure uniformity in the results of the study. By using these four instruments we covered most of the psychological and social as well as some or the physical domains of HRQoL, which increased the reliability of the results.

Despite the remarkable strength of this study, few limitations were non-avoidable. A well-known challenge in long-term studies is reducing loss to follow-up. The response rate among the living lung-transplant recipients after 10 years in our study was 25.8%, which is relatively low. We performed some additional analyses to prevent possible bias due to a large number of missing patients. Firstly we evaluated the demographic characteristics of patients who were censored due to the end of the study, lost to follow-up or died and compared these with a profile of the included patients. There were no salient differences in demographics between missed patients and ongoing participants at specific follow-up time points. We also compared the final assessment of HRQoL scores of patients who were censored, lost to follow-up or died with the scores of respondents who were still participating in the study at certain time points (Appendix 3). Again, no particular differences were found between the two groups. The total number of patients who were lost to follow-up after transplantation without a known reason was only 81 (25%). Due to the death registry of the participating hospitals we discerned that merely 7 of these patients died after they were lost to follow-up (median survival after last assessment: 2 years (IQR 1-4 years)). Accordingly, the majority of patients who were lost to follow-up were still alive during the time of the study (range till end of the study 1 to 5 years, median: 3 years (IQR 1-4 years)). Thus, the incidence of major post-transplant complications with high mortality rate is very limited among these patients. Therefore, we can at least conclude that there is no large systematic bias due to missing patients.

Another limitation of this study is that it lacks a control group. Having one would have enabled a more thorough evaluation of confounding variables like ageing and social changes during the follow-up period. A potential limitation is the use of conventional self-report instruments to score perceived HRQoL. These instruments may be susceptible to what is so called adaptation in chronically ill patients [47]. Moreover, NHP has limited ability to detect respiratory-related impacts on perceived HRQoL. Finally, in this study we examined important baseline characteristics that can affect the HRQoL of patients long term after LTx. Based on the research data we collected, we are not in the position to study the relationship of these factors and particular post-transplant factors (e.g. BOS

and chronic heart failure) by extending the analyses. Further studies are necessary to assess the causal pathways of these factors in HRQoL alteration.

In conclusion, in line with previous studies, this study showed that lung-transplant patients experience improvement in all domains of HRQoL within the first year after transplantation. Despite differences in survival and post-transplant immunosuppression treatment, their perceived improvement tends to remain relatively constant for the entire life span. This positive effect over such a long period of follow-up is reported here for the first time, convincingly demonstrating the long-term effectiveness of this treatment modality in patients with end-stage lung diseases.

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Appendix

Appendix 1. Independent determinants of longitudinal changes in STAI, Zung and VAS scores

	STAI			Zung			VAS		
	Estimate (SE)	p Value		Estimate (SE)	p Value		Estimate (SE)	p Value	
Gender									
Male	-2.077 (1.19)	0.081		-3.149 (1.23)	0.011		2.409 (1.89)	0.202	
Working	-2.972 (1.32)	0.024		-3.196 (1.32)	0.016		3.220 (1.99)	0.106	
Underlying medical disease									
Alpha1-anti trypsin deficiency	-1.297 (1.70)	0.445		-3.876 (1.73)	0.025		6.761 (2.80)	0.016	
COPD	1.110 (1.49)	0.457		0.688 (1.52)	0.650		1.128 (2.38)	0.636	
CF	-3.071 (1.58)	0.051		-5.321 (1.78)	0.003		7.915 (2.40)	0.001	
Age groups									
Young	-2.129 (1.61)	0.186		-2.902 (1.70)	0.087		3.876 (2.74)	0.157	
Middle-aged	-1.182 (1.67)	0.479		-2.211 (1.63)	0.176		0.611 (2.73)	0.823	
Married	-0.236 (1.53)	0.878		-1.071 (1.50)	0.476		1.455 (2.32)	0.531	
Type of immunosuppression									
Tacrolimus	0.75 (1.26)	0.953		2.085 (1.33)	0.119		0.845 (2.13)	0.692	

Variables considered in the GEE models: gender, working situation, underlying medical disease, age, marital status and immunosuppression after LTx.

**Appendix 2.** Independent determinants of longitudinal changes in NHP scores

	Energy		Pain		Emotion	
	Estimate (SE)	p Value	Estimate (SE)	p Value	Estimate (SE)	p Value
Gender						
Male	-8.858 (3.39)	0.009	-3.985 (2.19)	0.068	-3.132 (1.65)	0.058
Working	-3.288 (3.49)	0.346	-6.575 (1.69)	<0.001	-1.874 (1.71)	0.273
Underlying medical disease						
Alpha1-anti trypsin deficiency	-7.803 (4.93)	0.114	0.300 (3.38)	0.929	-4.306 (2.19)	0.049
COPD	-0.979 (4.51)	0.828	4.839 (2.99)	0.105	-0.213 (2.10)	0.919
CF	-10.201 (3.75)	0.007	-4.420 (1.71)	0.010	-3.417 (1.90)	0.072
Age groups						
Young	-0.778 (4.55)	0.864	-5.011 (2.65)	0.058	-2.966 (2.26)	0.190
Middle-aged	1.029 (4.80)	0.830	-1.565 (2.81)	0.578	-2.707 (2.29)	0.238
Married	-3.384 (4.50)	0.452	-1.183 (2.80)	0.673	-1.595 (2.04)	0.434
Type of immunosuppression						
Tacrolimus	-3.989 (3.79)	0.293	-1.105 (2.48)	0.656	0.139 (1.76)	0.937
	Sleep		Social isolation		Physical activity	
	Estimate (SE)	p Value	Estimate (SE)	p Value	Estimate (SE)	p Value
Gender						
Male	-5.817 (2.98)	0.051	-0.966 (1.29)	0.455	-5.440 (2.16)	0.012
Working	-5.400 (3.20)	0.091	-1.498 (1.22)	0.220	-8.081 (1.98)	0.000
Underlying medical disease						
Alpha1-anti trypsin deficiency	-1.470 (4.61)	0.750	-2.335 (1.96)	0.234	-8.675 (2.81)	0.002
COPD	1.888 (3.77)	0.617	1.520 (1.66)	0.361	1.440 (3.00)	0.632
CF	-11.403 (3.41)	0.001	-2.182 (1.30)	0.093	-11.873 (1.80)	<0.001
Age groups						
Young	-11.497 (4.52)	0.011	-1.045 (1.64)	0.523	-10.165 (3.09)	0.001
Middle-aged	-5.120 (4.55)	0.261	-0.620 (1.72)	0.718	-3.286 (3.30)	0.319
Married	-0.593 (3.87)	0.878	-1.965 (1.82)	0.280	1.167 (2.91)	0.689
Type of immunosuppression						
Tacrolimus	3.532 (3.13)	0.259	-0.041 (1.47)	0.978	0.751 (2.41)	0.755

**Appendix 3.** Difference in mean scores of patients that dropped-out and respondents on the 4 HRQoL instruments: difference of mean (*p value*)

	2nd year dropouts N=54	5th year dropouts N=19	10th year dropouts N=9	15th year dropouts N=10
STAI	1.8 (0.30)	5.1 (0.13)	3.2 (0.45)	-0.9 (0.83)
Zung	3.5 (0.07)	3.1 (0.31)	5.9 (0.16)	2.8 (0.57)
NHP Energy	9.5 (0.07)	12.1 (0.20)	28.5 (0.06)	9.3 (0.57)
NHP Pain	2.5 (0.39)	3.9 (0.44)	-2.5 (0.76)	-6.1 (0.39)
NHP Emotional reactions	2.3 (0.38)	6.6 (0.16)	2.3 (0.70)	5.3 (0.69)
NHP Sleep	-0.3 (0.94)	6.3 (0.37)	13.8 (0.22)	21.5 (0.12)
NHP Social isolation	1.3 (0.38)	1.9 (0.62)	-2.4 (0.36)	1.0 (0.85)
NHP Physical mobility	7.6 (0.06)	9.3 (0.21)	12.0 (0.16)	15.6 (0.15)
VAS	-5.7 (0.06)	-4.7 (0.33)	-6.7 (0.34)	-3.7 (0.63)



